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THE USE OF MIXED DIPHTHERIA-PERTUSSIS-TETANUS ANTIGENS *

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SYNOPSIS

The author reviews the use of mixed diphtheria-pertussis-tetanus antigens in the light of the information which has become available in recent years. When diphtheria toxoid and tetanus toxoid, adsorbed or unadsorbed, are added to either plain or adsorbed pertussis vaccine, a satisfactory level of diphtheria antitoxin can be obtained in children over 6 months of age and of tetanus antitoxin in children of any age. As to the duration of immunity, it appears that provided three doses of mixed antigens are given for the primary immunization of children 6 months old a substantial proportion will have effective antitoxin titres three years later, but that with two doses only the antitoxin levels fall more rapidly.

Reviewing the evidence, the author considers that mixed antigens will be useful in future immunization campaigns, although he makes it clear that extensive investigations, particularly on the immunizing effect of the pertussis component, must be undertaken before their value can be finally assessed.

The reactions to and complications after inoculation with mixed antigens are then discussed, particularly in relation to convulsions, encephalopathy, and poliomyelitis. Finally, the author considers provisional recommendations for the use of mixed antigens, pointing out that the main question in all countries is whether the advantages of giving all three antigens simultaneously to children under 6 month of age, necessary because of the pertussis mortality in the first months of life, outweigh the disadvantages.

Castellani was the first to mix antigens, but most of his work was carried out with mixed typhoid and paratyphoid A and B vaccines, which are of similar antigenic constitution, and it was Ramon,[30] in 1926, who first mixed a toxoid with a bacterial antigen. He found that the addition of diphtheria toxoid to typhoid vaccine increased the antitoxin response to the diphtheria component without interfering with the measurable antibodies to the typhoid component. As a result of his studies soldiers in the French army have been inoculated with a mixed diphtheria-TAB antigen since 1931 and with diphtheria-TAB-tetanus antigen since 1934.

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In 1940 the administration of mixed tetanus and diphtheria toxoids was made compulsory for all children reaching 1 year of age in France. Ramon reviewed his contributions and those of other French workers at the International Congress for Microbiology at Rome in 1953 and indicated that a high degree of success was achieved in military and civilian practice.

Bordet [4] in 1936 suggested that diphtheria toxoid could be added to pertussis vaccine and a similar suggestion was made by Ledingham [21] in 1939. Since then, and particularly in the past three years, numerous reports of studies in man and animals on toxoids mixed with pertussis vaccines have been published. Fleming [9] in a comprehensive review commented on the scattered nature of these investigations. He pointed out that on some important aspects information is scanty or entirely lacking and that comparison of the results of different observers, because of their varied approach, is difficult and unsatisfactory. Since Fleming's review further information has been obtained and as mixed antigens are now widely used for the immunization of children, especially in North America, a re-assessment of the situation is timely, though final conclusions on their place in immunization campaigns must be deferred until further investigations have been made.

The advantages of effectively mixing diphtheria, pertussis, and tetanus antigens are the reduction in the number of injections with a consequent simplification of administrative problems and the reduction of the cost of mass campaigns. A further advantage claimed is that the immunizing potency of the toxoids is increased without interference with the antibody-producing capacity of the vaccines. In considering the heightened potency of the toxoid components, however, a clear distinction must be made between plain (fluid, unadsorbed) toxoids and adsorbed toxoids.

Enhancement of the Potency of Plain Toxoids

MacLean & Holt [23] injected 66 adults either with tetanus toxoid alone or with tetanus toxoid mixed with TAB vaccine. Two doses of the toxoid or the mixed antigen were given at intervals of 4 or 6 weeks and serum samples were obtained 14 days after the last injection. The titres of tetanus antitoxin in the groups given the mixed antigen were about five times greater than those in the groups given the toxoid alone. The difference in the intervals between the injections made no difference to the antitoxin response. Mathieson [24] reported that in guinea-pigs diphtheria toxoid mixed with plain pertussis vaccine gave substantially greater protection than toxoid from the same batch, and Greenberg & Fleming [15, 16] confirmed his findings in extensive studies, also in guinea-pigs. Greenberg & Fleming also observed that the addition of tetanus toxoid to a mixture of diphtheria toxoid and pertussis vaccine further increased the diphtheria antitoxin response without reducing the tetanus antitoxin response. Fleming,

Greenberg & Beith [10] obtained similar results in children about 4 months of age given two injections of the antigens singly or in mixtures at 3-weekly intervals. On the other hand, Sauer & Tucker [32] in a study of 464 children between 8 and 24 months of age who were given three injections at 3-weekly intervals of diphtheria toxoid and pertussis vaccine, either mixed before injection or injected at the same time at different sites, found that the Schick-negative rates 6 weeks after the last injection were 98% in the one group and 95% in the other. Though no enhancement of potency with the mixed antigen was apparent, the Schick test is not delicate enough to show differences between antigens of high potency.

The evidence from studies in man and animals suggests that the efficacy of plain diphtheria or tetanus toxoid is generally enhanced when mixed with pertussis or TAB vaccines. Sauer & Tucker's findings may indicate, however, that with three doses of toxoid there is little difference in the level of immunity obtained with mixed and unmixed antigens, but serum antitoxin examinations at intervals would have given more accurate information on this point. Increased potency would appear to be due to the particulate nature of the vaccine. Numerous studies have shown that particulate matter as widely diverse as tapioca, milk, alum, and suspensions of colloids will increase the potency of a plain toxoid.

Effect on the Potency of Adsorbed Diphtheria Toxoid

There is very little evidence that mixing an adsorbed diphtheria toxoid with pertussis vaccine increases the immunizing potency of the toxoid. It is true that Ordman & Grasset [28] demonstrated in guinea-pigs that APT mixed with 30 000-50 000 million *Haemophilus pertussis* per ml gave higher antitoxin titres than plain toxoid of similar Lf content mixed with 20 000 million *H. pertussis*, but the mineral carrier in these experiments may not have been at the optimum concentration and the differing numbers of *H. pertussis* in the vaccines may also have had an effect. In field studies Bell [3] found that 10% of 236 children over 5 months of age were Schick-positive one year after two doses of APT compared with 3% of 271 children given two doses of adsorbed diphtheria-pertussis antigen, but here also the adequacy of the amount of the mineral carrier has to be considered. Schütze [34] found in guinea-pig experiments that, whereas the potency of diluted APT was increased when it was mixed with plain pertussis vaccine, no increase was noted when undiluted APT was mixed with the vaccine. In a recent study of PTAP (purified toxoid-aluminium phosphate precipitated) in England and Wales [14] 728 of 730 children (99.7%) were Schick-negative 10-14 weeks after the second dose. This suggests that, where a purified toxoid adsorbed on to the optimum amount of aluminium phosphate (10 mg per ml) is used, there is little room for further enhancement

of the potency of the toxoid (as judged by Schick-negative rates) when pertussis vaccine is added. On the other hand, it is clear that the potency of the adsorbed toxoid is not reduced by the addition of pertussis vaccine. For example, Simon & Craster [35] found 99% of 520 children between 6 months and 5 years of age Schick-negative 4 or more months after two doses of APT mixed with pertussis vaccine given at intervals of one or two months; Kendrick [19, 20] tested the serum antitoxin levels of 71 children 11-14 months after three doses of an adsorbed mixed antigen and all had 0.01 unit or more of antitoxin per ml; and Bousfield [5] Schick-tested 51 children one year after two doses of a PTAP-pertussis mixture followed by one dose of plain pertussis vaccine and found all of them Schick-negative.

Antitoxin Responses to Adsorbed Diphtheria and Adsorbed Tetanus Toxoids in Pertussis Vaccines

So far the addition of one toxoid, diphtheria or tetanus, to one vaccine, pertussis or TAB, has been considered. Though some of the evidence rests on small numbers of observations, the general findings are that in primary immunization the potency of plain toxoids, at least if given in not more than two doses, is increased when they are added to pertussis vaccine or TAB but that the potency of adsorbed toxoids is neither increased nor decreased.

Most recent studies have been made with " triple antigens ", in which the diphtheria and tetanus components have been adsorbed. Miller, Humber & Dowrie [26] injected children mainly 6-12 months old with a triple antigen, and gave two doses at 3-monthly intervals. Each dose contained 26-30 Lf adsorbed diphtheria toxoid, 100 000-120 000 minimum lethal doses (MLD) adsorbed tetanus toxoid and 20 000 million *H. pertussis*. Six months after the second dose all of 114 children tested were Schick-negative and 65% of 37 children had tetanus antitoxin titres of more than one unit per ml, and all had more than 0.01 unit per ml—the level they considered indicated protection.

Peterson and Christie [7, 29] began a study in 1944 in children from 4 weeks of age upwards. Some 2000 children were inoculated and 573 were followed up for 13 months. Three injections at 6-weekly intervals were given. The first and third contained adsorbed diphtheria toxoid (30 Lf) adsorbed tetanus toxoid (100 000 MLD) and adsorbed pertussis vaccine 20 000 million organisms per ml. The second dose consisted of 40 000 million *H. pertussis* adsorbed vaccine. The diphtheria antitoxin results are shown in Tables I and II. The titres were satisfactory in children over 6 months of age at the time of the first inoculation, but were less satisfactory in children under 6 months of age. The tetanus antitoxin titres were satisfactory at all ages; 96% of 573 children had titres of 0.1 unit or more at

TABLE I. DIPHTHERIA ANTITOXIN LEVELS AT DIFFERENT AGES 3 MONTHS AFTER THE LAST PRIMARY INOCULATION *

Number of children tested	Age (months)	Percentage with titres of	
		0.003 unit or more	0.03 unit or more
282	<3	81	58
86	3-5	98	82
53	6-11	100	91

* Based on data from Christie & Peterson.[7]

3 months after immunization and 98% had similar titres 13 months after immunization.

It is clear that with adsorbed diphtheria and tetanus toxoids added to plain or adsorbed pertussis vaccine, a satisfactory level of diphtheria antitoxin can be obtained at least in children over 6 months of age. With tetanus toxoid, satisfactory levels can apparently be obtained at any age, and as far as the evidence goes, it does not appear that mixing the toxoids interferes with the antitoxin response to each antigen in children who are being primarily immunized.

Duration of Antitoxic Immunity

Little information is available on the duration of antitoxin immunity. The most recent report is that by Volk, Top & Bunney.[37] They took blood samples from most of 251 children, all of whom were over 2 years of age when primarily immunized with a mixture of adsorbed toxoids and pertussis vaccine three years earlier. They compared antitoxin titres before and after reinforcing doses were administered. Of 201 children given three primary

TABLE II. DIPHTHERIA ANTITOXIN LEVELS AT DIFFERENT AGES 13 MONTHS AFTER THE LAST PRIMARY INOCULATION *

Number of children tested	Age (months)	Percentage with titres of	
		0.003 unit or more	0.03 unit or more
121	<3	69	42
49	3-5	80	55
36	6+	100	75

* Based on data from Christie & Peterson.[7]

inoculations 83% still had 0.1 or more unit of diphtheria antitoxin per ml of serum before the reinforcing dose; 3% had less than 0.001 unit. Of 45 children given only two primary inoculations only 28% had 0.1 unit per ml before the reinforcing dose was given. Examinations for tetanus antitoxin showed that 40% of those who received three primary inoculations had titres of 0.05 unit or more and 65% had titres of 0.02 unit or more before a reinforcing dose was given, but of those who received only two primary inoculations only 10% had titres of 0.05 unit and 30% titres of 0.02 unit per ml of serum. After the reinforcing dose was given, all responded quickly to both toxoids and six months later all children had more than 0.1 unit of diphtheria antitoxin and more than 0.05 unit of tetanus antitoxin. This evidence suggests that, provided three doses are given for primary immunization in children over 6 months of age, a substantial proportion will still have what are considered to be effective antitoxin titres three years later, but that after two doses both diphtheria and tetanus antitoxin levels fall more rapidly.

Immunity to Pertussis

Information based on serum antitoxin levels can reasonably be taken to give some indication of immunity to diphtheria and tetanus. With pertussis there is no satisfactory evidence that the level of the measurable antibodies—agglutinins, haemagglutinins, or complement-fixing antibodies—is related to immunity to the disease. Further, evidence based on antibody estimations may lead to unacceptable conclusions. Miller, Humber & Dowrie [26] and Miller & Ryan [27] were not satisfied with the agglutinin production after two doses of a triple antigen or after two doses of the triple antigen with an interposed injection of either 20 000-30 000 million or 40 000-60 000 million *H. pertussis*. Peterson and Christie [7, 29] concluded that 80 000 million *H. pertussis* adsorbed on to aluminium hydroxide was not enough to produce optimum immunity in any age-group. It is difficult to define optimum immunity but the British Medical Research Council studies [13] indicated that 60 000 million *H. pertussis*, without a mineral carrier, given in three divided doses reduced the secondary attack-rate in children exposed to infected siblings from 85% to 10% and resulted in a mild attack in 70% of those who developed symptoms. The assessment of immunity to pertussis must at present therefore be based on the results of field studies.

Bell [3] found that the attack-rate in 407 children 2-23 months of age given two doses of APT plus pertussis vaccine was 12% compared with 41% in 385 similar children given APT alone. Kendrick [20] gave 1326 children 6 months to 5 years of age one dose of plain pertussis vaccine followed in one week by one dose of APT plus pertussis vaccine; the dose of mixed antigens was repeated four weeks later. The children were followed

up after inoculation and the attack-rate in the vaccinated group was 1 per 100 person-years compared with 10 per 100 person-years in a group of 1511 unvaccinated controls. Simon & Craster [35] gave two doses of APT plus 10 000 million *H. pertussis* at intervals of one or two months to 840 children between 6 months and 5 years of age. They found, mainly by examining notification records, that 4 of 11 vaccinated children were attacked after home exposure compared with 26 of 29 unvaccinated children similarly exposed. These three studies, particularly that by Bell, which satisfied the most stringent criteria for strictly controlled studies, indicated that mixed APT-pertussis antigen reduced the incidence of pertussis in the vaccinated. Whether the mixed antigens were as effective as the pertussis vaccine would have been if given alone was not determined.

Interference between Antigens

Though the work so far reviewed has shown that the interference phenomenon described by earlier observers is of less practical significance than was thought, the careful studies in guinea-pigs recently reported by Barr & Llewellyn-Jones [2] have now to be considered. The authors demonstrated that when guinea-pigs already immune to diphtheria were immunized with mixed diphtheria-tetanus prophylactic the response to the tetanus component was significantly reduced. The reduction could be compensated for to some extent by increasing the dose of tetanus toxoid, but the response was still significantly lower than that of guinea-pigs not immune to diphtheria. The reduction in antitoxin response was not apparent if guinea-pigs previously immunized against diphtheria were first given an injection of tetanus toxoid alone and later an injection of mixed toxoids. If an injection of mixed toxoids was given first, however, and was followed by an injection of toxoid alone, the resulting reduction in response was of the same order as that obtained after two doses of the mixed toxoids. In a series of experiments with TAB vaccine and tetanus toxoid similar results were obtained.

These findings in animals cannot immediately be accepted as evidence of what happens in man, nor do we yet know whether mixtures of diphtheria toxoid and tetanus toxoid with pertussis vaccines will behave in the same way as mixtures of TAB and tetanus toxoid. Clearly, however, Barr & Llewellyn-Jones's work emphasizes the urgent need for more studies. If their findings are confirmed in children considerable care will have to be exercised in mixing antigens, especially if they are used for reinforcing doses or in children with a partial immunity to one antigen. If, for example, after primary immunization with mixed toxoids the immunity to tetanus waned more quickly than immunity to diphtheria, the effect of a mixed reinforcing dose might be to elicit a full and rapid diphtheria antitoxin response and this might crowd out the response to the tetanus toxoid com-

ponent. Again, if mixed antigens were given to reinforce immunity to diphtheria and to serve as the first dose in primary immunization against tetanus the diphtheria antitoxin response might crowd out the response to tetanus toxoid. Similar results might follow the use of toxoid in pertussis vaccine.

To summarize thus far, there is reasonably good evidence that mixed antigens will be useful in future immunization campaigns. But extensive carefully controlled investigations must be undertaken in man and animals before their value can be finally assessed. Studies are required on the problem of interference, on the duration of immunity with mixed and separate antigens, on the relative amounts of antigen required to give balanced antibody responses, and on dosage and the spacing of doses for primary immunization. We particularly require more information on the time intervals for reinforcing doses and on the importance of interference when mixed antigens are used for this purpose. Though many of these studies can be made by means of serological examinations, the evaluation of the pertussis component must still depend on controlled field trials in children who may be exposed to infection.

Reactions to Mixed Antigens

It is difficult to obtain sound information on the incidence of mild, local or general reactions and very few adequate comparisons between different antigens have ever been made. But there is general agreement that mixtures of unadsorbed antigens cause less local reaction than mixtures of adsorbed antigens. Sauer, Tucker & Markley [33] recommended plain mixtures in preference to adsorbed mixtures for this reason. Miller & Ryan [27] recorded that 0.3% of injections of an aluminium hydroxide adsorbed diphtheria-tetanus toxoid mixed with pertussis vaccine were followed by the occurrence of sterile abscesses, and Peterson and Christie [7, 29] reported about 12 abscesses or persistent nodules in 6000 inoculations. Butler (personal communication—1954) found that 14 of 170 subcutaneous inoculations with aluminium phosphate adsorbed diphtheria-pertussis antigen in children less than 1 month old were followed by sterile abscesses compared with 1 abscess in 200 incolulations of plain diphtheria-pertussis antigen. In children over 1 month old 9 of 214 inoculations with adsorbed antigens resulted in abscesses compared with no abscesses in 426 inoculations with plain mixed antigen. Hutchison [18] observed that 3% of 450 injections of a plain diphtheria-pertussis antigen containing 10 000 million organisms per ml were followed within 48 hours by areas of redness and swelling of less than 20 mm in diameter, whereas 17% of 449 inoculations of a similar antigen containing 20 000 million organisms per ml

were followed by local reactions of similar diameter and an additional 1.5% were followed by larger reactions. This tends to confirm the impression that the reactions with unadsorbed mixtures are mainly due to the bacterial component of the mixed antigen. It is probable that reactions with the unadsorbed mixed antigens are similar to those obtained with unadsorbed pertussis vaccine alone. Even with adsorbed mixed diphtheria-pertussis antigens, however, the degree of local reaction has seldom been sufficient to deter many parents from allowing the course of injections to be completed, but where all things are equal there is every reason to prefer the antigen which causes least local or general disturbance.

Complications after Mixed Antigens

No immunization procedure is entirely free from the risk of remote sequelae. In recent years the question of neurological complications has been the subject of many reports. Radiculitis in soldiers inoculated with vaccines or sera received prominence during the war years, but at present the problems which occupy most attention are the occurrence of convulsions and encephalopathies after pertussis vaccination and the reported association between inoculation and poliomyelitis with paralysis of the inoculated limb.

Convulsions and encephalopathy

Byers & Moll,[6] Toomey,[36] and Anderson & Morris [1] have shown that a child inoculated with pertussis vaccine alone or with a mixed vaccine containing *H. pertussis* may occasionally develop convulsions and may suffer severe and permanent cerebral damage. Such an occurrence must be extremely rare, and few immunologists or paediatricians now consider that the vaccination of healthy children should not be carried out for fear of this danger. There is some difference of opinion on the vaccination of children with a personal or close family history of epilepsy, convulsions, hydrocephalus, and similar conditions. Melin [25] has suggested that children suffering from convulsive disorders ought to be vaccinated as the risk after vaccination is said to be less than the risk after an attack of pertussis. In the Medical Research Council whooping cough vaccine trials in Great Britain, it was decided after the publication of Byers & Moll's paper [6] that children with a personal or family history of cerebral lesions should not be vaccinated. As the case described by Anderson & Morris [1] was in a child who had had a transient hemiplegia—probably due to mumps encephalitis—three months earlier, it was also decided not to inject children with a definite history of encephalitis, and to postpone vaccination in children recovering from specific virus infections or in presumed susceptible children exposed to such infections if still within the incubation period.

It seemed reasonable also not to inject a child who had been vaccinated against smallpox within the previous month. In the current trials an effort has been made to collect information on the incidence and severity of convulsions in the 20 000-30 000 children in the follow-up studies, and it is hoped to obtain information on the association in time between inoculations and convulsions. For the present it is probably wise to confine vaccination to children who are fit and well and who have no personal or family history of cerebral lesions, as the occurrence of cases of encephalopathy in children with such a history might well deter mothers of healthy children from consenting to have them injected.

Poliomyelitis and the Inoculation of Mixed Antigens

Since the observation by McCloskey [22] and Geffen [11] that an undue proportion of children with paralytic poliomyelitis had received an inoculation of diphtheria toxoid, pertussis vaccine, or mixed prophylactics, often in the paralysed limb within a month before the onset of symptoms, a number of reports confirming the association in time and site have been made. Grant [12] and Geffen [11] considered that the evidence in England indicated that the relationship was most evident when mixed adsorbed antigens were employed. A Medical Research Council committee has made further observations, but these have not yet been published. It may be significant that adsorbed mixed antigens are no longer favoured in England and that Rhodes [31] in a careful study of paralytic and non-paralytic cases of poliomyelitis failed to observe any relationship between inoculation and paralysis in epidemics in Canada where unadsorbed mixed antigens are usually employed. It is clearly important that more information on the relationship between poliomyelitis and separate or mixed antigens with or without mineral carriers should be obtained, and that some estimate should be made of the relative risks. For the present the recommendations of the World Health Organization Conference of Heads of Laboratories producing Diphtheria and Pertussis Vaccines [38] should be carried out. The Conference recommended that immunization and vaccination should normally be continued during the poliomyelitis season except in the presence of serious epidemics, when all immunization and vaccination should be temporarily suspended in the locality. Where the incidence of poliomyelitis was not of alarming proportions, immunization should continue but the use of mixed adsorbed antigens should be discouraged.

Provisional Recommendations for the Use of Mixed Antigens

Despite the many questions which have still to be answered on the advantages and disadvantages of mixed and separate antigens there is no doubt that mixed antigens will continue to be used on an increasing scale.

The relative importance of diphtheria, tetanus, and pertussis varies in different countries and a plan for the use of mixed antigens in one country would not necessarily be suitable for another. In England, for example, in 1952 there were only three cases of diphtheria, none of them fatal, in infants under 1 year of age. As diphtheria immunization is less effective in the first six months of life, when some infants may still have residual maternal antitoxin, than in the second six months, and as experience in Britain has shown that diphtheria can be controlled by primary immunization towards the end of the first year of life with a reinforcing dose at about 5 years of age, there is clearly no reason to change the present British plan for diphtheria immunization. On the other hand, in 1951, of the 273 deaths from whooping cough in England and Wales in children in the first year of age 158 (58%) were in children below 6 months of age and 87 of these (32% of the total) were in children under 3 months of age. Even if pertussis immunization is less effective in very young children there appears to be a case for early immunization, though it is difficult to see how it could be instituted early enough to prevent most of the deaths in children under 3 months of age. The case for early immunization may not be so strong as it appears at first sight. I have held that in families where the older children are immunized the young baby, who is most likely to be exposed to infection by an elder sibling, will be screened from exposure; on the other hand, immunized children with mild and sometimes almost unrecognizable attacks have occasionally infected younger unprotected siblings with serious results. At present, no community in Britain is well protected against whooping cough, and when a high level of immunization with effective antigens is attained it may be that pertussis will be eradicated much as diphtheria has been, but that is speculation, and babies under 6 months of age are liable to be exposed to risk for some time to come.

Tetanus in Britain is a rare disease. There are about 80 deaths each year of which about 30 are in children under 15 years of age, 3 of these being in the neonatal period.[8] Tetanus immunization would, provided reinforcing doses were given, prevent most of the deaths in children and no doubt lessen the number of deaths at older ages. If a system of recording could be devised to give general practitioners and hospital casualty officers information on the immunization state of injured persons, active immunization would also cut down the use of tetanus antitoxin and this might be its chief value.

The main question in all countries, however, is whether the advantages of giving all three antigens simultaneously to children under 6 months of age, which is necessary because of the mortality from pertussis in the first few months, outweigh the disadvantages. Research to answer this question has already been outlined but it may be asked whether, so far as present knowledge goes, better results might not be obtained by giving different combinations of antigens at different ages. For example, studies might be made on the efficacy of giving three doses of mixed tetanus-pertussis antigen at 2, 3,

and 4, or 3, 4, and 5 months, absorbed diphtheria toxoid alone at 7 and 8 months, and a reinforcing dose of tetanus-pertussis antigen at 11 or 12 months. Provided the tetanus toxoid did not interfere with the potency of the pertussis antigen, this plan would ensure that children were protected against pertussis early, and that diphtheria immunization was carried out at the age when the antitoxin response is known to be good and long-lasting. It would also ensure that both tetanus and pertussis immunity were reinforced in the first year of life, which all are agreed is necessary, and would have the advantage, important in some countries, that no inoculations would be required between the end of the first year and school entry at 5 years of age. At school entry immunity to all three diseases would have to be reinforced. If after investigation interference between antigenic responses was found to be less important in practice than Barr & Llewellyn-Jones's studies [2] at present suggest, a reinforcing dose of a suitably balanced triple antigen mixture might be given; otherwise one or all antigens might have to be given separately.

Assuming that the triple antigen could be used for reinforcing injections, a total of seven injections would be required in the first 5 years. This compares reasonably well with established practice in countries where triple antigens are now employed. In Canada, for example, four injections (including an early reinforcing dose at 6 months of age) are recommended for primary immunization, and three reinforcing doses are recommended before the child enters school—a total of seven injections. M. Greenberg [17] has recommended that in New York reinforcing doses of triple antigen should be given every three years so that at least six injections would be required before the child reached 6 years of age.

It should be stressed, however, that these suggestions are put forward for discussion and that such a plan should be employed only after experimental studies had been made in animals and children with particular reference to the antibody responses to each of the components of a mixed antigen used for reinforcing immunity. Finally, whether mixed or separate antigens are employed, immunity to diphtheria, and to tetanus where tetanus immunization is carried out, should be reinforced between 9 and 11 years of age, before the child leaves school.

RÉSUMÉ

Ramon fut le premier, en 1926, à mélanger une anatoxine avec un antigène bactérien. A la suite de ses recherches, les soldats de l'armée française ont été inoculés dès 1931 par un antigène mixte (diphtérie-TAB) et depuis 1934 par un mélange d'antigènes (diphtérie-TAB-tétanos). En 1940, l'inoculation d'anatoxines mixtes (diphtérie-tétanos) a été rendue obligatoire, en France, pour les enfants d'un an. En 1936, Bordet suggéra l'addition d'anatoxine diphtérique au vaccin anticoquelucheux. Cette idée fut soutenue par Ledingham en 1939. Actuellement, l'usage des antigènes mixtes est très répandu, en

particulier en Amérique du Nord. Aussi est-il opportun de faire le point de la situation, bien que l'on ne puisse définir encore exactement le rôle que ces antigènes seront appelés à jouer dans les campagnes de vaccination.

Les vaccins mixtes permettent de réduire le nombre des injections, et par conséquent les formalités administratives et les frais. D'autre part, les études faites sur l'homme et l'animal indiquent que, lors de la primo-immunisation — en deux doses —, l'efficacité des anatoxines diphtérique ou tétanique simples est généralement exaltée par la présence de vaccin anticoquelucheux ou de TAB. L'activité des anatoxines adsorbées n'est ni diminuée ni augmentée.

Plus récemment, des études ont été entreprises avec trois antigènes (diphtérie-tétanos-coqueluche), les deux anatoxines étant sous forme adsorbées. Il ne semble pas que le fait de mélanger les anatoxines altère la réponse antitoxique à chacun des antigènes, lors de la primo-immunisation. On ne possède que peu de données sur la durée de l'immunité antitoxique. D'après les études faites, une forte proportion des enfants de plus de six mois ayant reçu trois doses d'antigènes présentaient encore un titre protecteur élevé trois ans après la primo-immunisation. Si l'inoculation est limitée à deux doses, les titres antitoxiques baissent rapidement.

Si les titres antitoxiques du sérum peuvent être considérés comme une indication du niveau d'immunité acquis contre la diphtérie et le tétanos, rien ne prouve que le titre en agglutinines, hémagglutinines, anticorps fixateurs du complément soit un indice du degré d'immunité contre la coqueluche. Pour le moment, seules des études pratiques permettent d'estimer la valeur des vaccins anticoquelucheux.

D'autres problèmes restent à résoudre : l'interférence entre les antigènes composant le mélange, la durée de l'immunité conférée par les antigènes mixtes d'une part et les antigènes isolés, d'autre part; la dose minimum des divers antigènes nécessaire à une réponse sérologique équilibrée; l'intervalle entre les injections de primo-immunisation; l'intervalle entre les doses de rappel et l'interférence éventuelle lorsqu'on utilise des antigènes mixtes pour ces dernières. Un certain nombre de ces études pourront être effectuées par des méthodes sérologiques, mais pour l'antigène coquelucheux il faudra recourir à des études pratiques contrôlées sur des enfants.

Aucun procédé d'immunisation n'échappe au risque de réactions postvaccinales. Le problème le plus actuel dans ce domaine est l'éventualité de convulsions et d'encéphalopathies à la suite de la vaccination anticoquelucheuse et la coïncidence que l'on a signalée entre cette vaccination et la poliomyélite — avec parfois paralysie du membre sur lequel l'injection a été pratiquée. Tant que la relation entre vaccination et encéphalopathie n'est pas élucidée, il est préférable de limiter la vaccination aux enfants sains, en excluant ceux qui ont des cas de lésions cérébrales dans leur ascendance ou qui en ont été eux-mêmes atteints. Quant aux risques de paralysie poliomyélitique, la Conférence des chefs de laboratoires préparant des vaccins antidiphtériques et anticoquelucheux a recommandé que la vaccination anticoquelucheuse soit poursuivie pendant la saison de la poliomyélite, sauf en cas d'épidémie, où toutes les vaccinations seront suspendues temporairement dans la localité. Mais l'emploi d'antigènes mixtes adsorbés est à déconseiller à ce moment.

Malgré les inconnues qui subsistent, il est certain que les antigènes mixtes seront employés de plus en plus couramment. L'importance relative de la diphtérie, du tétanos et de la coqueluche varie d'une région à l'autre et chaque pays adaptera ses programmes à ses conditions propres. La question principale, pour chaque pays, est de déterminer si les avantages de l'inoculation d'antigènes mixtes à des enfants de moins de six mois — nécessaire en raison de la forte mortalité causée par la coqueluche durant les six premiers mois de la vie — surpassent les désavantages. On peut se demander si l'on n'obtiendrait pas de meilleurs résultats en donnant diverses combinaisons d'antigènes à des âges différents, telles que : trois doses d'antigènes mixtes (tétanos-coqueluche) à 2, 3, 4 mois ou à 3, 4, 5 mois; l'anatoxine diphtérique seule à 7 et 8 mois et une dose de rappel tétanos-

coqueluche à 11 ou 12 mois. Si l'on admet que l'anatoxine tétanique ne nuit pas à l'activité du vaccin coquelucheux, ce schéma de vaccination assurerait une protection précoce contre la coqueluche, une immunité diphtérique à l'âge où la réponse immunologique est bonne et durable. On assurerait ainsi un renforcement de l'immunité contre le tétanos et la coqueluche durant la première année. Ce schéma aurait en outre l'avantage de ne pas exiger d'inoculation entre la fin de la première et la cinquième année. A l'âge où l'enfant entre à l'école, l'immunisation contre les trois maladies devra être renforcée, soit sous forme mixte si l'interférence est jugée insignifiante, soit sous forme isolée. Qu'il s'agisse d'antigènes mixtes ou isolés, l'immunisation contre le tétanos et la diphtérie sera renforcée encore une fois entre 9 et 11 ans.

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